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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/716,169	12/17/1996	STEPHEN M. ANDERTON	961125	5487

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THE WEBB LAW FIRM, P.C.
700 KOPPERS BUILDING
436 SEVENTH AVENUE
PITTSBURGH, PA 15219

EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
11/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/716,169	ANDERTON ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008 and 13 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,28,29 and 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,28,29 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of the peptide species: LSTLVXN, with traverse, in the paper filed 8/13/08 is acknowledged.

Upon reconsideration the restriction requirement has been withdrawn.

2. Claims 24, 28, 29, 31, 32, and new Claims 33-36 are being acted upon.

3. Applicant's amendment and remarks, filed 2/22/08, are acknowledged.

4. In view of Applicant's amendment the previous rejection under the first paragraph of 35 U.S.C. 112 for the introduction of new matter into the claims has been withdrawn.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 24, 28, 29, 31, 32, and new Claims 33-36 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the method of the instant claims would function as claimed.

As set forth previously, A review of the specification reveals only that preimmunization of Lewis rats with a peptide consisting of *M. tuberculosis* hsp65 86-100 provided a barely noticeable reduction in adjuvant-induced arthritis (AA) severity, and preimmunization of Lewis rats with a peptide consisting of *M. tuberculosis* hsp65 256-270 provided a more substantial reduction in both AA and CP20961-induced arthritis severity. It is unclear how these minimal showings can enable a method of treating *all* Th1-mediated inflammatory diseases in *all* species including humans.

First note that *no* treatment whatsoever of *any* disease is disclosed. It is well-established that preimmunization to prevent or reduce the severity of many diseases can be effective whereas actual treatment of established disease is not,

e.g., rabies or experimental prevention of other autoimmune diseases such as diabetes and EAE. Also note that the specification at page 28 teaches that the reduction in severity of AA is absolutely MHC dependant, i.e., RT1.D^{l} restricted. Accordingly, it is unclear how this treatment could be expected to work in the outbred human population whose MHC differences vary significantly more than do the Lewis rat's. Further note that the peptides of the instant claims, *M. tuberculosis* hsp65 81-100 and 241-270 are not even the peptides of the examples, i.e., they are larger. Given that the claims encompass the use of peptides comprising as few as 5 amino acids of *M. tuberculosis* hsp65 81-100 or 241-270, a peptide comprising, for example, hsp65 241-246 (for which there has been no showing of any sort of efficacy) might be encompassed for use in the method of the instant claims (if it could be shown that the fragment had a "corresponding mammalian stress protein homologue").

Also note that the mechanism by which the claimed method would function was not well understood. Indeed, the discussion at pages 27-28 discloses only that, "the hypothesis is that the mechanism by which hsp65 preimmunisation protects Lewis rats against arthritis is based on activation of T cells that recognise an epitope shared with rat hsp60. Recognition by these T cells of elevated levels of the self epitope presented by MHC class II expressing cells at the site of inflammation (the joint) would then provide an antigen-specific mechanism for regulation of the inflammatory process." There is no discussion of the induction of T regulatory cells which the Inventors now argue is the invention. Finally, the specification provides no reason why the method of the instant claims would be expected to be effective against any and all Th1-mediated inflammatory diseases.

Regarding the use of APLs for the treatment of autoimmune disease, Anderton (2001, of record), teaches that,

> "This unpredictability [of APLs] led us to argue against the use of antagonist or immune deviating APL in human autoimmune disorders" (page 370).

The reference goes on to teach that APL administration to humans can be dangerous and that in at least one case a human trial was suspended due to adverse reactions in a significant number of patients. Note that this is the Inventors' own work. While it might be argued that the hsp65 peptides of the instant claims are not APLs *per se*, the peptides administered in the claimed method require only a 5 amino acid identity with *M. tuberculosis* hsp65, thus from 2-25 amino acids may vary. In this case the peptides would indeed functionally comprise APLs.

As set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses no data representative of the broad method of the instant claims, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 2/22/08, have been fully considered but are not found persuasive. Applicant argues that working examples are not required and that the specification does show "protection after preimmunization".

While working examples are not required, a specification enabling for the reasonable scope of the claims is required. Given that the claims encompass the treatment of *any* inflammatory disease, in *any* species, with an essentially *unlimited* number of APLs, the minimal showing that a certain very specific model of arthritis can be reduced in a specific inbred strain of rats after preimmunization (note that preimmunization is not treatment of ongoing disease), with a specific peptide that is *not* an APL, cannot be considered to be representative nor enabling for the broadly claimed method.

Applicant submits and cites van Peijvelde [sic] et al. (2007) and Kamphius et al. (2005) in support of the claimed method.

First note that the references were published some 11 and 13 years post-priority date (respectively) and thus provide no enablement for the invention at the time of filing. Regardless, the references still comprise insufficient enablement for the claimed method. First, neither references employ APLs in their experiments. Accordingly, they can provide no enablement for the claimed method. Also note that Kamphius et al. (2005) merely reports the finding of peptide epitopes capable of inducing *in vitro* T cell responses. This most certainly is not representative of, nor enabling for, the method of the instant claims. Regarding Puijvelde et al. (2007), the reference teaches the *pretreatment* of a highly inbred strain of experimental mice before the induction of disease. Again, this is not the method of the instant claims.

Applicant argues that an understanding of a mechanism by which an invention functions is not required.

Applicant's statement is indeed correct. However, if breadth beyond what is disclosed is sought, then a reasonable method for ascertaining what a reasonable breadth would be, i.e., an understanding of the mechanism of the claimed invention, would be helpful. Absent such an understanding, it is unclear how the skilled artisan could predict whether or not the broadly claimed invention could function without undue experimentation.

Applicant argues, "Anderton et al. … does not relate to the predictability within the art. Anderton is directed to an altered peptide ligand."

A review of the new claims shows the administration of peptides comprising "X" "wherein X is any amino acid, i.e., the administration of APLs.

7. Claims 24, 28, 29, 31, 32, and new Claims 33-36 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

As set forth previously, There is insufficient written description to show that Applicant was in possession of "a peptide of 7-30 amino acids having the sequence of a part of the amino acid sequence of a mycobacterial protein having a conserved mammalian stress protein homologue, said part comprising at least 5 amino acids which are identical with the corresponding amino acids in the same relative position in one of the sequences 81-100 and 241-270 of SEQ ID NO. 1 representing the sequence of the stress protein hsp65 of *Mycobacterium tuberculosis*, at least 4 consecutive amino acids of said at least 5 amino acids being identical with the corresponding mammalian stress protein amino acids amino acids". Note that while the peptides employed in the claimed method are fragments of SEQ ID NO:1, to establish which fragments are encompassed for use in the instant claims their "corresponding" "mammalian stress protein homologues" must be described.

An adequate written description of the peptides employed in the method of the claims would require either an adequate description of a common function *and* structure, or a disclosure of a representative number of species. A review of the definition of "stress proteins" at page 2 of the specification shows that they encompass "enzymes or proteins that exhibit a raised level of synthesis during inflammation or other stress stimuli in cells residing at the site of such inflammation or stress condition", including heat shock proteins, interleukins and interferons. While some attempt is made at disclosing a common cause of induction, no common structural or functional features are disclosed. Indeed, it is well-established that heat shock proteins and interleukins do *not* share a common structure or function. Given these facts, one of skill in the art would

conclude that the specification fails to disclose either a representative number of species (just one, *M. tuberculosis* hsp65 241-270 presumably corresponding to human hsp65) or common functional and structural characteristics, adequate to describe the peptides required for use in the method of the instant claims. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

Applicant's arguments, filed 2/22/08, have been fully considered but are not found persuasive. Applicant argues that the instant amendment obviates the rejection.

It is noted that the claims still encompass an essentially unlimited number of peptides, none of which are shown to be capable of being used to treat or protect against an inflammatory disease. Accordingly the rejection has been maintained.

8. The following are new grounds for rejection necessitated by Applicant's amendment.

9. Claims 24, 28, 29, 31, 32, and new Claims 33-36 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a written description rejection for the introduction of new matter into the claims.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) the method of Claim 24 employing the recited peptides,

B) the method of Claim 36 employing a second peptide.

Applicant has not cited support for the new limitations and none has been found.

Applicant has traversed a previous rejection which comprised some limitations that have been retained in amended Claim 24.

Regarding the 7-30 amino acid limitation, Applicant pages 6 and 8 of the specification.

Page 6 disclosed peptide of from 5-30 amino acids, "identical to the microbial sequence". These are not the 7-30 amino acid APLs of the instant claims. Page 8 discloses

peptides of SEQ ID NO:1 with "… 7 amino acids with the same relative position as those in the hsp65 T cell epitopes". While it is unclear precisely what this peptide encompasses, it is not the peptide of the instant claims.

10. No claim is allowed.

11. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, Ph.D. can be reached on (571) 272-0841.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/G.R. Ewoldt/
G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600